DETAILED ACTION

1. This office action is in response to an amendment filed June 20, 2011. Claims 67-106 were previously pending, with claims 72-75, 81, 82, 87, 89, 92, 97, 99 104 and 106 withdrawn from consideration. Applicants cancelled claims 67, 69, 77-83, 85, 87 and 90, and amended claims 68, 70-76, 84, 88, 89, 91-93, 95, 96, 100, 103, 105. Claims 68, 70, 71, 76, 84, 88, 91, 93-96, 98, 100-103 and 105 will be examined.

2. Applicants' claim cancellations obviated the previously presented rejections for claims 67, 69, 77-80, 83, 85 and 90. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

Response to Arguments

3. Applicant's arguments filed June 20, 2011 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 68, 70, 71, 76, 84, 88, 91, 93-96 and 98 under 35 U.S.C. 103(a) over Saito et al. as evidenced by Heid et al. and the GenBank sequence with accession No. X98077, Higashi et al., Stoll-Becker et al., Su et al. and Buck et al., Applicants argue the following:

i) "Clear error is manifest, first of all, by the rejection reliance on the unsupported finding (Office Action, page 17) (emphasis added): "Since the claimed primers simply represent structural homologs...derived from sequences suggested by the prior art...the claimed primers and probes are *prima facie* obvious over the cited references." Nothing of record---other than PTO allegations--supports the so-called structural homology represented by the presently claimed primers.

All the PTO can, and does, show--to support the alleged structural homology represented by the presently claimed primers--is some overlap between (1) the presently claimed sequences and (2)

the prior art sequences. No evidence is put forward---only bare PTO allegations---that equates some sequence overlap with structurally homologous sequences, rendering the rejection fatally flawed. "The Examiner bears the initial burden...of presenting a *prima facie* ease of unpatentability" and "the ultimate, burden of persuasion on the issue," .In re Oetiker, 24 USPQ2d 1443, 1444 and " 1447 (Fed. Cir. 1992), which burden the "Examiner can satisfy. . . only by showing some objective teaching in the prior art," Exparte Obukowicz, 27 USPQ2d 1063, 1065 (BPA&I 1992), and "the evidence upon which the examiner relies must dearly indicate that a worker of routine skill in this art would view the claimed invention as being obvious." Exparte Welters, 214 USPQ 735, 736 (BPA&I 1982) (emphasis added). "It is facts which must support the legal conclusion of obviousness," Exparte Crissy, 201 USPQ 689, 695 (POBdApp 1976) (emphasis added), and the PTO "may not ....resort to speculation, unfounded assumptions or bindsight reconstruction to supply deficiencies in the factual basis. In re Warner, 154 USPQ 173, 178 (CCPA 1967) (*emphasis original*). An argument by the PTO "is not prior art." In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Simply put, there is no evidence showing the differences between (1) the presently claimed sequences and (2) the prior art Sequences--i.e., the non-overlapping sequences--are mere structurally homologous differences, as alleged in the rejection.

Moreover, mere overlap between the claimed subject matter and the prior art is insufficient to establish the obviousness of the claimed subject matter absent. *Ex Parte Wittpenn*, 16 USPQ2d 1730, 1731 (BPA&I 1990). As held by the Board, "the Examiner's conclusion lacks any logical foundation... [there being] no disclosure within the reference that would have led the routineer to make the critical selections to arrive at the claimed [subject matter]." 16 USPQ2d at 1731.

Similarly here, as in *Wittpenn* (16 USPQ2d at 1731), the rejection cites "no disclosure within the reference that would have led the routineer to make the critical [sequence] selection [from Saito]

to arrive at the claimed [sequences]." Accordingly, "in the absence of some motivation to select" the presently claimed sequences, "the Examiner's conclusion lacks any logical foundation" and, so,"the rejection ....cannot be sustained." *Wittpenn*, 16 USPQ2d at 1731. See *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious"). See also *In re Belle*, 26 USPQ2d 1529 (Fed. Cir. 1993), and *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992)."

ii) "Clear error is also manifest by the rejection relying on "it would have been *prima facie* obvious to one of ordinary skill in the art...to have used the sequences, of the HBV genome to design primers and probes for the detection of the genome with a high expeetation of success" (emphasis added, page 16 of the Office Action). Even assuming, arguendo, the prior art provided a high expectation of successful functionality, as alleged in the rejection, the "high expectation of success" falls short of the mark.

It is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure. *In re Mills,* 16 USPQ2d 1430, 1433 (Fed. Cir. 1990). *See In re Swinehart,* !69 USPQ 226 (CCPA 1971). As explained above, all that the PTO can rely on in the cited prior art--to describe or suggest structure of the presently claimed sequences--is some sequence overlap; which overlap, "in the absence of some motivation to select" the presently claimed sequences, "lacks any logical foundation." *Wittpenn,* 16 USPQ2d at 1731."

iii) "Clear error is manifest, with all due respect, in the PTO reliance on the Supreme Court decision *KSR International Co. v. Teleflex, Inc.,* 550 U.S. 398 (2007). As set forth in the statement of rejection, itself (Office Action, page 7), "in [a] case where there is a limited number of possibilities, 'obvious to try' is obvious" under *KSR*. However, no such limited number of

possibilities exists in the present case. Even taking as correct the 285 possible primers (i.e., "95 control primers...represent 113 of all possible primers") alleged in the statement of rejection (OfficeAction, page 18), 285 is hardly the limited number of possibilities envisioned by the Supreme Court in *KSR*.

Moreover, with all due respect, the rejection reliance on *In re Kubin,* no. 2009-1184, slip op. April 3, 2009, is misplaced, *since Kubin* is not in point. The rejection devotes about two full pages of text to repeating (apparently verbatim) the reasoning set forth by the *Kubin* court in affirming a §103 rejection in which "the record shows repeatedly that [prior art] Valiante's Example 12 produces....the claimed polynucleotide" *(Kubin,* slip op. page 8) (emphasis added). As Opposed to the facts in *Kubin,* and as admitted in instant rejection, itself (Office Action, page 16) (emphasis added), prior art "Saito et al. do not teach primers... [even] comprising... SEQ ID NO: 2, 3 or 8," let alone "consisting of SEQ ID NO: 2, 3 or 8," as presently claimed, rendering the rejection untenable. *In re Thrift,* 63 USPQ2d 2002, 2008 (Fed. Cir. 2002) ("a ground of rejection is simply inadequate on its face...[when] the cited references do not support each limitation of [each] claim")."

iv) "Furthermore, even taking everything in the rejection as correct, arguendo, the rejection is overcome. That is, "the absence of secondary considerations," upon which relies "the claimed primers...[being] *prima facie* obvious over the cited references" (Office Action, page 17), is remedied by the Rule 132 declaration of the inventor, Marie-Phillippe Biron, provided herewith. As explained in file Rule 132 declaration (and precied below) the presently claimed oligonucleotide sequences exhibit surprising and unexpected results.

The Rule 132 declaration reports and discusses data obtained in tests comparing each of the primers of sequence SEQ ID NO: 2 and SEQ ID NO: 3, according to the presently claimed

invention, with structurally close primers-named "Sequence 2a" and "Sequence 3a" in the Rule 132 declaration---described in the international patent application WO 93/13120, of record (cited in the International Search Report of PCT/IB 2004/004022). As set forth in the declaration (paragraph bridging pages 6 and 7), the "Sequence 2a" and "Sequence 3a" are even closer to the presently claimed sequences than those found in the cited references.

Based on the data obtained, the Rule 132 declaration (pages 4 and 6) concludes, *i.a.,*

> The sequences SEQ ID NO: 2 and Sequence 2a are...both complementary sequences of the HBV genome and they hybridize to a single common region on the genome of HBV. However, SEQ ID NO: 2 has unexpected and advantageous properties compared to Sequence 2a....Given the results obtained with Sequence 3a it is completely unexpected that SEQ ID NO: 3 is suitable for real-time PCR. SEQ ID NO: 3 has therefore unexpected properties.

Additionally, the Rule 132 declaration shows, contrary to the PTO finding, any primer of any length complementary to any segment of the HBV genome is not suitable for sensitive detection of hepatitis B viruses of several genotypes and, moreover, small changes in the primer nucleotide sequence can significantly affect sensitivity. As set forth in the Rule 132 declaration, itself (page 6), based on the data obtained,

> a primer including the sequence of another primec while being complementary to the genome to be amplified, may lead to different and less advantageous amplification results. Thus, two sequences close to each other do not have intrinsically the same properties.

In view of the foregoing remarks, the rejection of claims 67-71, 76-80, 83-86, 88, 90, 91, 93-96 and 98 under 35 U.S.C. §103(a), as allegedly being unpatentable over Saito, Heid, GenBank sequence, Higashi, Stoll-Beeker, Su and Buck,. is overcome. Withdrawal of the rejection is in order."

Regarding i), the obviousness rejection, as explained in the "Response to Arguments" section of the previous office action, contrary to Applicant's argument that the rejection contains "unsupported finding" and that "No evidence is put forward---only bare PTO allegations", the rejection is based on the following facts:

The positions of primers and probes for all of the references were mapped to a single HBV genome sequence, with GenBank Accession No. X98077, to facilitate discussion. The following table summarizes the positions of primers, probes and amplicons produced using either Applicant's oligonucleotides or oligonucleotides used in the prior art:

Reference	Primer-forward	Primer-reverse	Probe	Amplicon
Instant claims	1440-1457	1582-1602	1527-1548	1440-1602
Saito et al.	1414-1435	1728-1744	1681-1705	1414-1744
Higashi et al.	1433-1455	1588-1610		1433-1610
Su et al.	1561-1580	1755-1774		1561-1774
Stoll-Becker et al.	1380-1401	1529-1550		1380-1550

The following conclusions are based on the results of amplification with the above primers used in the prior art:

a) The region of the X gene between bp 1380 to 1774 can be successfully amplified using different combinations of primers.

b) The region amplified by instantly claimed primers lies entirely within the region successfully amplified by Saito et al. and overlaps between bp 1440-1550 with the region amplified by primers of Stoll-Becker et al.

c) The region amplified by instant primers is entirely encompassed by the region amplified by Higashi et al., and only 15 bp shorter than amplicon generated by the primers of Higashi et al. Further, the forward primer of Higashi et al. overlaps with the instant primer over bp 1440-1455, i.e., 16 of the 18 bp, and the reverse primer of Higashi et al. overlaps with the instant primer over bp 1588-1602, i.e., 15 of the 21 bp (emphasis added).

Therefore, the obviousness rejection is based on factual state of the art at the time of the invention, when the sequences of hundreds of HBV isolates were known, as were the techniques for selecting primers and probes for DNA amplification, both by PCR and its variants, such as real-time PCR and quantitative real-time PCR. Applicant is directed to the review of Mackay et al. (Nucl. Acids Res., vol. 30, pp. 1292-1305, 2002), describing in detail applications of real-time PCR specifically in virology, detailing the different techniques, including quantitative real-time PCR, and 209 references detailing amplification of different viruses by PCR, real-time PCR and quantitative real-time PCR. In conclusion, the rejection is based on the enabling disclosure of the references cited in the rejection and the state of the art at the time of the invention was filed.

In addition, Applicant's reliance on *In re Wittipenn* for most of the arguments is not persuasive. The situation presented in that case was concerned with the following claimed composition:

"1. A mild surfactant composition having good foaming characteristics and such non-irritating characteristics that it is suitable for use on perioccular surface tissues, comprising:

(a) an anionic surfactant having high foaming properties and being mildly irritating to human tissues; said surfactant being present in cleansing quantities;
(b) a nonionic surfactant in an amount capable of reducing the irritant properties of said anionic surfactant and capable of emulsifying or solubilizing body surface physiologic debris; and
(c) an induced nonionic surfactant in an amount sufficient to enhance the foaming properties of the anionic and nonionic surfactants while further reducing the irritating characteristics of the anionic surfactant,
(d) the pH of said composition being maintained substantially in neutrality, at which said last-named surfactant is induced to act as a nonionic surfactant rather than shown the ionic properties it exhibits in an acid medium.
2. A surfactant composition as claimed in claim 1, in which said induced nonionic surfactant is an amine oxide."

The rejection was not supported by the Board because:

"We shall not sustain the rejection before us. At claim 1 of Roggenkamp, the patentee defines a composition containing about 1 to about 10% by weight of an amine oxide and 5 to about 50% by weight of a non-interfering auxiliary anionic surfactant. Although the patent, at column 5, discloses that the composition may also contain a nonionic surfactant, the reference further teaches that the composition may contain cationic and amphoteric surfactants. However, no preference is indicated for any particular component. Thus, there is no apparent basis for the examiner's conclusion that the claimed composition would have been *prima facie* obvious. It will be appreciated that the present situation does not involve the mere combination of components for the same purpose that each would individually be used."

Therefore, the cited case does not apply to the instant situation, which has nothing to do with a chemical composition, in a situation where the sequence from which the primer sequences can be selected is known, where there are several specific teachings of the amplification of the sequence using specific primers and where one of ordinary skill in the art would have at least a region with known sequence to start from. For example, it is clear that Saito et al. successfully amplified a region between bp 1414-1728, encompassing a region amplified by the instantly claimed primers, as does Higashi et al. Therefore one of ordinary skill in the art at the time of the invention, instead of kicking an open door, would have a good starting point for designing primers to amplify a fragment of the X protein gene using primers of Higashi et al., for example.

ii) Regarding the expectation of success, the law only requires "reasonable expectation of success", which does not require experimental proof that what is suggested by a reference would work.

The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success .... [T]he expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

"If a person of ordinary skill can implement a predictable variation [of a known work], § 103 likely bars its patentability." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007)."

The statement indicating "high expectation of success" is based on the fact that Higashi et al. successfully amplified a region 15 bp longer than one amplified by instant primers, and Saito et al. successfully amplified a 330 bp region using real-time amplification. Therefore, one of ordinary skill in the art at the time of the invention would have had at least a reasonable expectation of success of choosing at least one primer for amplification of the X protein gene.

Regarding iii), there is definitely a limited number of possibilities in this case. To start with, one could simply design primers based on the primers of Higashi et al. Even assuming that one would have to deal with the region of 330 bp taught by Saito et al., the number of 15 bp primers would be 316. Further, taking into account the fact that nobody designs primers by hand, using the primer-design software would greatly simplify the process. Finally, primer design is not an inventive process, but a routine optimization. Therefore, based on the desired amplification conditions and desired amplicon length, it would have been *prima facie* obvious to one of ordinary skill in the art to design primers with claimed sequences.

Regarding iv), Dr. Biron presented the following evidence:

1) amplification of HBV-containing sample using primer pairs with SEQ ID NO: 2, SEQ ID NO: 3 and probe with SEQ ID NO: 12,

2) amplification of HBV-containing sample using primer pairs with SEQ ID NO: 2a (corresponding to SEQ ID NO: 13 of WO 93/13120), SEQ ID NO: 3 and probe with SEQ ID NO: 12,

3) amplification of HBV-containing sample using primer pairs with SEQ ID NO: 2, SEQ ID NO: 3a (corresponding to SEQ ID NO: 13 of U.S. Patent No. 5,877,162) and probe with SEQ ID NO: 12.

Dr. Biron concluded that (page 4 of the declaration, first paragraph; page 5, fifth and last paragraph; page 6, first paragraph):

"Similar results were obtained for primers on both targets. However, whereas for genotypes A to F, the concentrations measured with SEQ ID NO: 2 and Sequence 2a are not considered significantly different (the difference between the 2 concentrations is less than 0.5), quantification of the genotype G is significantly different using SEQ ID NO: 2 and Sequence 2a, the value obtained with SEQ ID NO: 2 being the closest to the expected concentration."

"The results obtained indicate that sequence 3a is not suited for real-time PCR."

"Indeed, no coherent result (coefficient of correlation of 0.265) could be obtained using Sequence 3a for the HBV genotype A Accurun® panel dilution."

In addition, no result could be obtained for the detection of genotypes A to G with sequence 3a, while SEQ ID NO: 3 yielded results close to the expected values…"

However, there are several problems with the conclusion of unexpected results based on the data presented by Dr. Biron.

i) The results are not commensurate in scope with the claimed subject matter. They were obtained using a combination of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 12 as a probe. There are no claims corresponding in scope to the declaration.

For example, claim 88 is drawn to a set of oligonucleotides comprising

(a) a set of oligonucleotides according to claim 84 and

(b) an oligonucleotide having a length of 15 to 40 nucleotides and including a sequence selected from, the group consisting of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, and sequences fully complementary thereto.

Claim 84 is drawn to a set of oligonucleotides consisting of

- an oligonucleotide consisting of SEQ ID NO: 2 and
- at least one oligonucleotide selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, and SEQ ID NO: 7.

Therefore, none of the claims require the particular combination of three oligonucleotides for which the results presented by Dr. Biron were obtained.

ii) The results were obtained using oligonucleotides which would not be chosen by one of ordinary skill in the art to represent primers to be combined with SEQ ID NO: 2 and 3.

Specifically, the sequences of the “2a” and "3a” "primers” were never intended to be primers. The "2a” sequence, or SEQ ID NO: 13 from the WO 93/13120 publication was designed as a probe to detect HBV sequences. The “3a” sequence, or SEQ ID NO: 13 from the U.S. Patent No.

5,877,162 was designed as an RNAse P probe in an assay to detect HBV (see legend to Fig. 10 and 11:

"FIG. 10 is a diagram of the structure formed by hybridization of a SEGS (HBV H) with the nucleotide sequence SEQ ID NO. 12 to a portion HBV RNA corresponding to nucleotides 1559-1606 of a 2.1 kb HBV RNA (SEQ ID NO. 13). The SEGS and HBV RNA are aligned to show the base pairing which forms a structure similar to the A stem and T stem of tRNA. The RNAse P cleavage site is indicated with an arrow.

FIG. 11 is a diagram of the structure formed by hybridization of a SEGS (HBV H1) with the nucleotide sequence SEQ ID NO. 14 to a portion HBV RNA corresponding to nucleotides 1562-1606 of a 2.1 kb HBV RNA (nucleotides 4-48 of SEQ ID NO. 13). The SEGS and HBV RNA are aligned to show the base pairing which forms a structure similar to the A stem and T stem of tRNA. The RNAse P cleavage site is indicated with an arrow."

One could argue that a sequence is a sequence, therefore what it is designed for does not matter. However, if one is to compare results of an amplification experiment which uses two primers, one should, as known to one of ordinary skill in the art, compare apples to apples. In the instant case, the primers "2a" and "3a" do not function properly because they would not be expected to based on the 30 years of accumulated knowledge of PCR primer design. Let us look at the sequences and melting temperatures of the primers used in Dr. Biron's experiments.

SEQ ID NO: 2: 5' GCT GAA TCC CGC GGA CGA 3'

18 bp, 12 G+C, 6 A+T; the melting temperature (simplified method): Tm = 12 x 4° C + 6 x 2° C = **60° C**.

SEQ ID NO: 3: 5' GTG CAG AGG TGM GCG MGT G 3' (as listed in the specification), the sequence used by Dr. Biron: 5' GTG CAG AGG TGA AGC GAA GTG 3'(the underlined bases differ from SEQ ID NO: 3).

24 bp, 12 G+C, 8 A+T; the melting temperature (simplified method): Tm = 12 x 4° C + 8 x 2° C = **64° C**.

SEQ ID 2a: 5' GGC GCT GAA TCC YGC GGA CGA CCC BTC TCG 3'

30 bp, 22 G+C (Y = C and B = C), 8 A+T; the melting temperature (simplified method): Tm = 22 x 4° C + 8 x 2° C = **104° C**.

SEQ ID 3a: 5' ACG TGC AGA GGT GAA GCG AAG TGC ACA CGG TCC GGC AGA TGA GAA GGC 3'

48 bp, 29 G+C, 18 A+T; the melting temperature (simplified method): Tm = 29 x 4° C + 18 x 2° C = **152° C**.

Therefore, in the amplification with the primer pair SEQ ID NO: 2 and SEQ ID NO: 3, the Tms of the primers were 60° C and 64° C, not ideal, but pretty well matched. In an experiment with SEQ ID 2a and SEQ ID NO: 3, the Tms of the primers were 104° C and 64° C, therefore, the Tm of the forward primer was 40° C above that of the reverse primer (which one of ordinary skill in the art would not have chosen), yet the amplification still worked very well (which seems to support examiner's conclusions about primer selection). Finally, in the amplification using the pair SEQ ID NO: 2 and SEQ ID 3a, the Tms of the primers were 60° C and 152° C (emphasis added). Clearly, without even performing the amplification, one of ordinary skill in the art at the time of the invention would be able to tell that the amplification using primers with SEQ ID NO: 2 and SEQ ID

3a would not work (and it did not). Therefore, the conclusions derived by Dr. Biron from the above experiments do not support the conclusion of unexpected results: they support a conclusion that unmatched amplification primers do not work.

For the reasons cited above the declaration of Dr. Biron is insufficient to overcome the previously presented rejections.

B) Regarding the rejection of claims 100-103 and 105 under 35 U.S.C. 103(a) over Saito et al. as evidenced by Heid et al. and the GenBank sequence with accession No. X98077, Higashi et al., Stoll-Becker et al., Su et al. and Buck et al., further in view of Pasupuletti and Stratagene Catalog, Applicant argues that since the rejection of claim 84 cannot be maintained, this rejection is improper.

The arguments regarding the rejection of claim 84, among others, were addressed above. The rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 68, 70, 71, 76, 84, 88, 91, 93-96 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office action) and the GenBank sequence with accession No. X98077 (1997; cited in the previous

office action), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002; cited in the previous office action), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997; cited in the previous office action), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) As a reference for further discussion, the positions of claimed SEQ ID NO: 2, 3 and 8 with respect to the HBV genome with GenBank accession No. are as follows (see BLAST alignment): SEQ ID NO: 2; bp 1440-1457; SEQ ID NO: 3: bp 1582-1602; SEQ ID NO: 8: bp 1527-1548.

Regarding claims 68, 70, 71, 84, 88 and 91, Saito et al. teach a set of three DNA oligonucleotides, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claim 76, Saito et al. teach the use of oligonucleotides to detect HBV (page 326, last paragraph; page 327, first paragraph); since the primers hybridize to the HBV, the method of claim 36 is anticipated.

Regarding claim 93, Saito et al. teach a method comprising:

a) contacting a set of oligonucleotides according to claim 43 with a biological sample or nucleic acid preparation obtained from a biological sample, under conditions suitable for the

oligonucleotides to hybridize to a HBV nucleic acid present in the sample (page 326, last paragraph; page 327, first paragraph);

b) amplifying said HBV nucleic acid using said oligonucleotides as primers (page 326, last paragraph; page 327, first paragraph);

c) detecting the amplification product, indicative of the presence of a HBV in the biological sample (page 326, last paragraph; page 327, first paragraph).

Regarding claim 94, Saito et al. teach PCR (page 326, last paragraph).

Regarding claims 95, 96 and 98, Saito et al. teach a probe for the X gene of HBV virus (page 326, last paragraph), which hybridizes to the bp 1681-1705 of the GenBank accession No. X98077. Saito et al. teach that the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide comprising a fluorophore and a quencher.

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

The expectation of success of using alternative primers derived from the sequence is provided by the references listed below.

Higashi et al. amplified HBV virus X protein by PCR using two sets of primers (page 375, paragraphs 5-9). These primers hybridize to the following regions of the X98077 sequence (see BLAST alignment): OAL-X1: bp 1433-1455, OAL-X4: bp 1588-1610. These primers create an amplicon which is shifted 5' with respect to the instant amplicon by 7 bp.

Stoll-Becker et al. teach detection of HBV X gene by PCR using primers P1 and P2 (page 5400, sixth paragraph; Table 1), which hybridize to the following regions of the X98077 sequence (see BLAST alignment): P1: bp 1380-1401, P2: bp 1529-1550. Therefore the amplicon generated by the primers of Stoll-Becker et al. overlaps with the amplicon generated by the instant primers between bp 1440-1550.

Finally, Su et al. teach amplification of the HBV virus in circulation of infected patients by PCR using primers directed to the X gene (page 2006, paragraphs 5 and 6), txs3 and xas1. As can

be seen from the alignment of the txs3 primer with the GenBank sequence X98077, the txs3 primer hybridizes to a region between bp 1561-1580, i.e., within the amplicon generated by the instant primers.

As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

6. Claims 100-103 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. (J. Med. Virol., vol. 58, pp. 325-331, 1999; cited in the previous office action) as

evidenced by Heid et al. (Genome Res., vol. 6, pp. 986-994, 1996; cited in the previous office action) and the GenBank sequence with accession No. X98077 (1997; cited in the previous office action), Higashi et al. (Liver, vol. 22, pp. 374-379, October 2002; cited in the previous office action), Stoll-Becker et al. (J. Virol., vol. 71, pp. 5399-5407, 1997; cited in the previous office action), Su et al. (Clin. Cancer Res., vol. 7, pp. 2005-2015, 2001; cited in the previous office action), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), Pasupuletti et al. (U.S. Patent No. 6,635,428 B2; cited in the previous office action) and Stratagene Catalog (p. 39, 1988; cited in the previous office action).

Regarding claims 100, 101, 103 and 105, Saito et al. teach a set of three oligonucleotides, two primers and a probe, each between 15 and 40 bp long, for the detection of the X gene of HBV (page 326, last paragraph). The position of these primers and probe are as follows with respect to the HBV wild-type genome sequence with GenBank accession No. X98077 (see BLAST alignment of these sequences): the first primer hybridizes between bp 1414-1435 of that sequence, the second primer with bp 1728-1744, and the probe with bp 1681-1705. Therefore, the amplicon produced by Saito et al. overlaps with the amplicon produced by the instant primers between bp 1440-1602, i.e., the amplicon produced using the instant primers is 100% contained within the amplicon produced by the primers of Saito et al.

Regarding claims 103 and 105, Saito et al. teach the probes were TaqMan probes according to Heid et al. (page 325, second paragraph). As evidenced by Heid et al., TaqMan probes comprise a fluorophore and a quencher (page 987, second and third paragraph), anticipating the limitations of an oligonucleotide being detectably labeled.

Regarding claim 102, Saito et al. teach PCR (page 326, last paragraph).

B) Saito et al. do not specifically teach primers and probes 15-40 bp in length comprising or consisting of SEQ ID NO: 2, 3 or 8.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the known sequences of the HBV genome to design primers and probes for the detection of the genome with a high expectation of success. In *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of HBV virus, and in particular for the detection of the X protein, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

The expectation of success of using alternative primers derived from the sequence is provided by the references listed below.

Higashi et al. amplified HBV virus X protein by PCR using two sets of primers (page 375, paragraphs 5-9). These primers hybridize to the following regions of the X98077 sequence (see

BLAST alignment): OAL-X1: bp 1433-1455, OAL-X4: bp 1588-1610. These primers create an amplicon which is shifted 5' with respect to the instant amplicon by 7 bp.

Stoll-Becker et al. teach detection of HBV X gene by PCR using primers P1 and P2 (page 5400, sixth paragraph; Table 1), which hybridize to the following regions of the X98077 sequence (see BLAST alignment): P1: bp 1380-1401, P2: bp 1529-1550. Therefore the amplicon generated by the primers of Stoll-Becker et al. overlaps with the amplicon generated by the instant primers between bp 1440-1550.

Finally, Su et al. teach amplification of the HBV virus in circulation of infected patients by PCR using primers directed to the X gene (page 2006, paragraphs 5 and 6), txs3 and xas1. As can be seen from the alignment of the txs3 primer with the GenBank sequence X98077, the txs3 primer hybridizes to a region between bp 1561-1580, i.e., within the amplicon generated by the instant primers.

As can be seen from the above references, selection of primers from the different and overlapping regions of the X gene produced successful amplification of the HVB sequences.

Buck et al. expressly provides evidence of the equivalence of primers in support of the above conclusion regarding primer selection from a known sequence. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see

page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

C) None of the above references teaches kits.

D) Regarding claims 100-103 and 105 Pasupuletti et al. teach kits for the PCR detection of HBV in real-time (col. 5, lines 64-67; col. 6, lines 1-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to package the primers and probes for the detection of HBV by the methods of Saito et al., Higashi et al., Stoll-Becker et al., Su et al. and Buck et al. as suggested by Pasupuletti et al. Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

7. No claims are allowed.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
September 7, 2011